differentiation of the parotid and submaxillary gland has been observed with isoproterenol treatment. The effect is most marked in parotid, where acini develop much earlier than in the litter-mate controls and striated ducts earlier become more abundant. The effects of isoproterenol on differentiation are separable from the influence of the drug on cell size.

1. Selye, H., Veilleux, R., Cantin, M., *Science,* 1961, v133, 44.

2. Brown-Grant, K., *Nature,* 196, 191, 1076.

3. Schneyer, C. A., *Am. J. Physiol.,* 1962, v203, 232.

4. Wells, H., Munson, P. L., *ibid.,* 1960, v199, 63.

5. Jacoby, F., Leeson, C. R., *J. Anat.,* 1959, v93, 201.

6. Schneyer, C. A., Schneyer, L. H., *Am. J. Physiol.,* 1961, v201, 939.

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Effect of Drug Infusion on the Splanchnic Circulation. I. Angiotensin Infusion in Normal and Cirrhotic Subjects. (28030)

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The physiology and pharmacology of angiotensin have recently been reviewed(1). Although there is considerable literature on its effect on cardiac output, blood pressure and peripheral resistances, there are few data on the effects of angiotensin on regional hemodynamics and, particularly, on splanchnic circulation. Abell and Page(2) noted a narrowing of the mesenteric vessels after angiotensin. Barer(3) found mesenteric blood flow to be reduced in the cat after single injections of 0.2 to 0.4 γ. Mandel and Sapirstein(4) could not observe in rats, under infusion of angiotensin at different rates, any significant variation in splenic and intestinal blood flow.

The present communication concerns the effects of intravenous infusion of angiotensin on splanchnic hemodynamics in normal and cirrhotic subjects.

Material, methods and procedure. The subjects were divided into 2 groups. Group I consisted of 8 subjects without liver and cardiovascular disease; Group II consisted of 7 patients with liver cirrhosis and portal hypertension.

After catheterization of a main right hepatic vein, hepatic blood flow (EHBF) was measured by a constant infusion of Indocyanine Green, following the Fick principle (5). At least 4 pairs of arterial and hepatic venous blood samples were obtained for estimation of basal hepatic blood flow.

Mean arterial pressure (MAP) was frequently recorded using a Rangoni-Battaglia electromanometer; the tracings were electrically damped.

The intrasplenic pressure (ISP) and the wedged and free hepatic vein pressures (WHVP and FHVP) were, alternatively, simultaneously recorded by a couple of Rangoni-Battaglia electromanometers with zero reference point 5 cm below the sternal angle. They were repeatedly recorded before and during the angiotensin infusion.

Portal venous pressure (PVP) was calculated from the formula:

$$\text{PVP (mm Hg)} = \frac{\text{ISP} + \text{WHVP}}{2}$$

or was assumed to equal the WHVP.

Splanchnic resistances (SR) were calculated from the formula:

$$\text{SR (dynes/sec/cm}^{-5}) = \frac{(\text{MAP} - \text{PVP}) \times 80}{\text{EHBF (l/min)}} (6).$$

Cardiac output (CO) was measured by an indicator dilution technic, using 10 μc of RISA. It was measured before and during the angiotensin infusion.

The rate of intravenous infusion of angio-

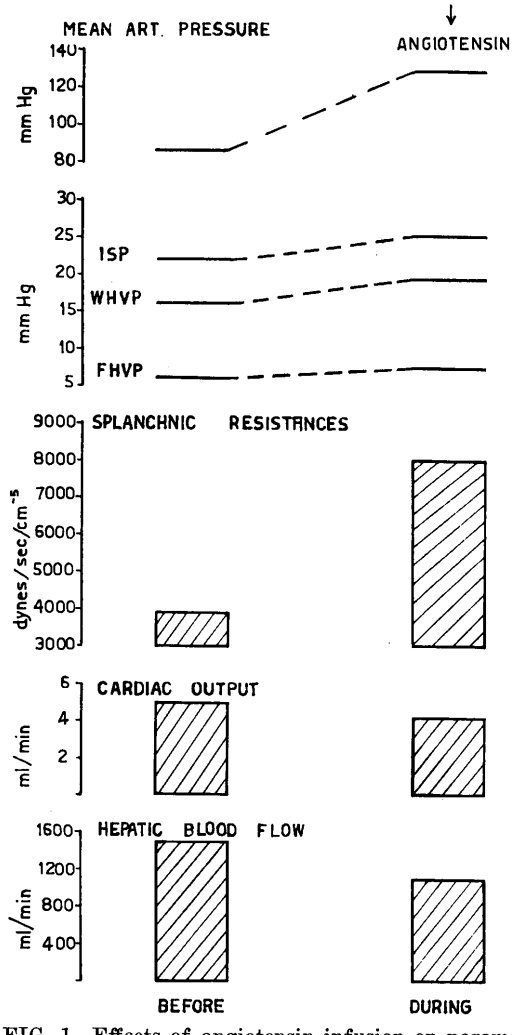

FIG. 1. Effects of angiotensin infusion on parameters of the splanchnic circulation.

tensin* was regulated on its pressor effect, in order to get a 50% rise in mean arterial pressure in all subjects. It ranged from 0.3 to 0.5 γ/kg/min. After a 20 minute interval 4 paired samples of blood were obtained, a pair every 5 minutes, for hepatic blood flow estimation.

Results. (Fig. 1). Mean arterial pressure: rate of angiotensin infusion was based on a 50% rise in mean arterial pressure. The rise was highly significant in both groups ($P < 0.001$).

Cardiac output was significantly reduced ($P < 0.001$) in both groups. In Group I the average reduction was 17.0%, in Group II 17.2%. On the whole it was reduced from 5090 to 4198 ml/min.

Estimated hepatic blood flow was in both groups significantly reduced ($P < 0.001$). In Group I there was a reduction of 29.2%, from 1709 to 1181 ml/min, in Group II of 17.8%, from 1244 to 1035 ml/min.

Intrasplenic and hepatic venous pressures: in a few subjects a moderate rise in pressure was observed, but averages were not statistically significant ($P > 0.05$).

Splanchnic resistances were greatly raised in all the subjects of both groups; the over-all average was 118.3% ($P < 0.001$).

Discussion. The calculation of splanchnic resistances depends upon the assumptions that estimated hepatic blood flow equals splanchnic blood flow and the measured indirect portal pressure corresponds to the pressure on the venous side of the mesenteric vessels(6). In patients with portal hypertension and portal collateral circulation the calculated splanchnic resistances are overestimated. Nevertheless the percentage changes induced by angiotensin are probably valid measures of the changes in splanchnic resistances.

Most of the pharmacological effects of angiotensin have been studied after single injections of the drug. They vary with the basal arterial pressure, the dose, and greatly differ from those obtained in constant infusion experiments(4). Because of greatly different individual sensitivity to the drug, we based its rate of infusion on its pressor effect; it ranged from 0.3 to 0.5 γ/kg/min. Cardiac output was significantly reduced, as previously reported(7,8,9,10,11). Estimated hepatic blood flow was also reduced significantly, and to a greater extent than the cardiac output. As a result of splanchnic arterioles vasoconstriction, splanchnic resistances were greatly raised.

The over-all circulatory effect of angiotensin appeared to be a slight reduction of cardiac output and a redistribution of blood flow through the organism. The reported increase in skeletal, muscle, cerebral and myocardial

* Hypertensin, CIBA.

blood flow(4,12) probably accounts for the reduction in the skin(12), renal(3,4,11,13) and splanchnic blood flow.

Summary. The effect on splanchnic circulation of a constant infusion of angiotensin was investigated on 8 normal subjects and 7 cirrhotic patients with portal hypertension. The rate of angiotensin infusion was varied to obtain a rise in mean arterial pressure of 50% and ranged from 0.3 to 0.5 γ/kg/min. Both cardiac output and estimated hepatic blood flow were reduced, respectively, by 17.5 and 23.9%. Portal venous pressure remained unchanged. Splanchnic resistances increased by 118.3%. These effects were present in the subjects of both groups.

1. Page, J. H., Bumpus, F. M., *Physiol. Rev.*, 1961, v41, 331.

2. Abell, R. G., Page, I. H., *J. Exp. Med.*, 1942, v75, 305.

3. Barer, G. R., *J. Physiol.*, 1961, v156, 49.

4. Mandel, J. M., Sapirstein, L. A., *Circulation Res.*, 1962, v10, 807.

5. Caesar, J., Shaldon, S., Chiandussi, L., Guevara, L., Sherlock, S., *Clin. Sci.*, 1961, v21, 43.

6. Shaldon, S., Dolle, W., Guevara, L., Iber, F. L., Sherlock, S., *Circulation*, 1961, v24, 797.

7. Taylor, R. D., Page, I., *Am. J. Med. Sci.*, 1943, v205, 66.

8. Wilkins, R. W., Duncan, C. N., *J. Clin. Invest.*, 1941, v20, 721.

9. Bradley, S. E., Parker, B., *ibid.*, 1941, v20, 715.

10. Cournand, A., Ranges, H. A., Riley, R. L., *ibid.*, 1942, v21, 287.

11. Finnerty, F. A., Jr., Massaro, G. D., Chupkovich, V., Tuckman, J., *Circulation Res.*, 1961, v9, 256.

12. Bock, K. D., Krecke, H. J., Kuhn, H. M., *Klin. Wchnschr.*, 1958, v36, 254.

13. Assali, N. S., Westersten, A., *Circulation Res.*, 1961, v9, 189.

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Effect of Drug Infusion on Splanchnic Circulation. II. Serotonin Infusion In Normal and Cirrhotic Subjects. (28031)

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The 5-hydroxy-tryptamine or serotonin is a very recently discovered and isolated hormone(1) and its physiological properties are not yet well known. Small amounts of 5-HT (2-8 γ/kg) can produce, besides a raised pulse rate, a slight rise or a slight fall in blood pressure or even a biphasic reaction(2): larger amounts (10-100 γ/kg) are usually hypertensive(3). Andrews and Butterworth (4), on histological grounds, suggested that serotonin may constrict the hepatic vascular bed. Gibertini(5), by single injections of serotonin (100 γ/kg) into a peripheral vein or directly into the portal vein of dogs, could observe, 30-40 seconds after the injection, a rise in portal pressure, lasting 3-4 minutes. Recently a raised blood level of serotonin was found in 28 patients with portal hypertension(6). It seemed that these two findings might be related. Hence the present studies of the effect of serotonin intravenous infusion on the splanchnic hemodynamics in normal and cirrhotic subjects were undertaken.

Material and procedure. The subjects were divided into 2 groups. Group I consisted of 8 subjects without liver and cardiovascular disease. Group II consisted of 8 patients with liver cirrhosis and portal hypertension.

After catheterization of a main right hepatic vein, hepatic blood flow (EHBF) was measured by a constant infusion of Indocyanine Green, following the Fick principle (5). At least 4 pairs of arterious and hepatic venous blood samples were obtained for estimation of basal hepatic blood flow.

Mean arterial pressure (MAP) was very often recorded by a Rangoni-Battaglia electromanometer; the tracings were electrically damped.